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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/334,325	06/16/1999	STEWART A. CEDERHOLM-WILLIAMS	CV0276A	5209

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 04/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/334,325	CEDERHOLM-WILLIAMS, STEWART A.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2003 and 11 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 13-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Upon further consideration of the present invention and for the completeness of the 35 U.S.C. 112 first paragraph rejection, the finality of the Official action mailed 9-8-03 has been withdrawn.

Applicant's amendment filed 11-7-03 and appeal brief filed 2-11-04 have been entered. Claims 2-12 and 17 have been canceled. Claims 1 and 13-16 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1 and 13-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for transforming a cell *in vitro* by applying a nucleic acid to the cell and then adhering a pliable, adhesive fibrin gel to said cell so as to entrap the nucleic acid in the fibrin gel to the cell, does not reasonably provide enablement for a method of transforming a cell *in vivo* by applying a nucleic acid to the cell and then adhering a pliable, adhesive fibrin gel to said cell so as to entrap the nucleic acid in the fibrin gel to the cell and transform said cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1 and 13-16 are directed to a method of transforming a cell *in vitro* or *in vivo* by applying, in order, a nucleic acid, such as a plasmid or the nucleic acid is incorporated in a virus, to the cell, a pliable and adhesive fibrin gel to the cell so a to entrap a transformation effective amount of the nucleic acid in the fibrin gel adhered to the cell. Claim 15 specifies the pliable, adhesive fibrin gel is formed by mixing a fibrin monomer composition with a polymerizing agent and the cell is contacted with the mixture while the mixture is pliable and adhesive. Claim 16 specifies the fibrin monomer composition comprises acid-solubilized fibrin and the polymerizing agent comprises a base effective to neutralize the mixture to form fibrin polymer.

The specification discloses the preparation of preferred sealant compositions and the incorporation of nucleic acid into fibrin gel, but fails to provide an enabling disclosure for the method of using fibrin monomer or fibrinogen that forms fibrin gel for genetic transformation of any nucleic acid or virus containing said nucleic acid at any location of a subject *in vivo*. The specification is directed to a method of transforming a cell *in vivo*. The claims read on applying a nucleic acid to a cell and then applying a pliable, adhesive fibrin gel to said cell so as to transform the cell *in vivo* at any location of any subject including human beings, mammals, fishes, birds, insects, fungus, plants etc.

The specification fails to provide adequate guidance and evidence for transforming a cell *in vivo* by applying a nucleic acid, such as a vector or a virus carrying the nucleic acid, to the cell first and then applying a pliable, adhesive fibrin gel to said cell so as to transform the cell *in vivo* at any location of any subject. No teachings are present within the specification in regard to how to transform cells in a subject with any nucleic acid in any vector or any virus containing said nucleic acid by the claimed method steps.

The claims read on applying a nucleic acid to cells in vivo so as to transform cells and the transformation of cells in vivo must have a use, which is to provide therapeutic effect in vivo. The title of the present invention reads "Fibrin sealant as a transfection /transformation vehicle for gene therapy". Therefore, the claims read on gene therapy in vivo. The state of the art for gene therapy *in vivo* was unpredictable at the time of the invention. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate resolution of the problem of vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression...The use of viruses (viral vectors) is powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells, However, humans

have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses." (e.g. p. 239, column 3).

Further, Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract). In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to transform a cell *in vivo* with any nucleic acid and a pliable, adhesive fibrin gel via various administration routes so as to provide therapeutic effects in an individual for a particular disease or disorder.

The specification also fails to provide adequate guidance and evidence for how to administer a pliable, adhesive fibrin gel to a cell having administered nucleic acid in a subject such that target cells in said subject are transformed with said nucleic acid. The specification

fails to provide adequate guidance for how to deliver the pliable, adhesive fibrin gel before the fibrin gel is polymerized to target cells in a subject for transformation of said cells. It was known in the art that the pliable, adhesive fibrin gel will polymerize quickly. The specification indicates that "Generally, the sealant mixture remains conveniently pliable for about 30 seconds or less" (page 17, lines 16, 17). Since the pliable, adhesive fibrin gel will polymerize in a short period of time, one would need to deliver said fibrin gel to target cells at various locations in a subject before polymerization of said fibrin gel so as to transform said target cells with a nucleic acid. This would be problematic because there is not much time for one skilled in the art to deliver the pliable and adhesive fibrin gel to the target cells inside the body of the subject, such as cells in liver, kidney, heart intestine, stomach etc, before the pliable and adhesive fibrin gel is polymerized. When the pliable and adhesive fibrin gel is polymerized before it reaches the target cells, the nucleic acid on the cells would not be entrapped in the fibrin gel and the target cells could not be transformed with said nucleic acid. There is no evidence of record that shows transformation of target cells in a subject with any nucleic acid via administering the nucleic acid to the cells first and then administering the pliable and adhesive fibrin gel to said cells.

The quantity of experimentation needed to make or use the present invention includes trail and error experimentation to determine how to administer a nucleic acid to the target cell on the surface of a subject or to the target cell at various locations inside the body of a subject, such as liver, kidney, lung, intestine, stomach etc., trial and error experimentation to administer the pliable and adhesive fibrin gel to the target cell on the surface of a subject or to the target cell at various locations inside the body of a subject, such as liver, kidney, lung, intestine, stomach etc., before the fibrin gel get polymerized so as to transform the target cell with said nucleic acid, and

trial and error experimentation to transform target cells with the claimed method such that therapeutic effects can be obtained for a particular disease or disorder in vivo.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Applicant argues that the specification teaches how to make the transforming composition and that transforming nucleic acids are well-known and one of ordinary skill knows how to measure transformation (brief, page 4). This is not found persuasive for the reasons set forth above. The claims read on gene therapy *in vivo*, however, specification fails to provide an enabling disclosure for the method of using fibrin monomer or fibrinogen that forms fibrin gel for genetic transformation of any nucleic acid or virus containing said nucleic acid at any location of a subject *in vivo*. Further, as discussed above, the state of the art for gene therapy *in vivo* was unpredictable at the time of the invention. Although it was known how to measure transformation efficiency, however, the specification fails to provide adequate guidance for how to deliver the pliable, adhesive fibrin gel before the fibrin gel is polymerized to target cells in a subject for transformation of said cells.

Applicant argues that transforming a cell *in vivo* is enabled when done with certain equipment (brief, page 4). This is not found persuasive for of the reasons set forth above and because the administration method disclosed in the previously cited Donovan reference is

different from the method of the presently claimed invention, thus, the previously cited Donovan reference is irrelevant to the presently claimed method.

Applicant argues that the 35 U.S.C. 112 first paragraph enablement rejection is related to 35 U.S.C. 101 rejection and the Office does not follow the Utility Examination Guidelines (brief, pages 4-6). This is not found persuasive because the 35 U.S.C. 112 first paragraph enablement rejection is **not** a 35 U.S.C. 101 rejection. Applicant fails to provide arguments directed to the 35 U.S.C. 112 first paragraph enablement rejection. Applicant's argument regarding the 35 U.S.C. 101 rejection is irrelevant to the 35 U.S.C. 112 first paragraph rejection. The claimed invention is not enabled for the reasons set forth above under 35 U.S.C. 112 first paragraph rejection.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

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